REMARKS

Claims 55, 56, 57, 58, 59, 60, 61, 62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89, 90, 91, 103, 104, 105, 106 are pending. Claims 1-54, 63, 66, 68-70, 72-78, 80, 82, 84, 86, 88, and 92-102 are cancelled. Claims 55, 57, 60, 90, 104, and 106 are amended. Support for the amendments can be found throughout the specification and claims as filed and as indicated below.

Drawings and Specification

The Examiner alleges that the drawings filed on April 10, 2010 are ambiguous because one reference numeral "5" for substrate is used for several different kinds of structures. Applicants respectfully disagree. The claimed microfluidic system comprises a substrate which comprises various features of the system. The substrate is the base material from which the microfluidic device is formed and, therefore, all the claimed microfluidic devices have substrate. According to the Patent Rules, "[t]he same part of an invention appearing in more than one view of the drawing must always be designated by the same reference character. . ." 37 C.F.R. § 1.84(p)(4). In Figure 3, the substrate is correctly indicated as numeral (5) which does not indicate the holder that holds multiple patch claim electrodes as suggested by the Examiner. In Figure 6, numeral (3) refers to the entire Nanoelectrode array not the substrate. Applicants have submitted a replacement Figure 6 herewith that indicates the Nanoelectrode array with brackets and have labeled the substrate as (5). In Figure 10A, the numeral (5) indicates the substrate that surrounds the microfluidics channel, the numeral (5) does not indicate the channel; indeed, the channel is indicated by numeral (8). Similarly, in Figure 10B, the numeral (5) indicates the substrate that surrounds the channel, it does not indicate a lid of a measurement chamber. In Figure 11, the numeral (5) correctly indicates the substrate in which the channels have been formed. Similarly, in Figures 13 and 14 the numeral (5) indicates the substrate from which the device has been formed. The Examiner is incorrectly redefining substrate to be separate and distinct structures and not the base material from which the device is made. The amendments suggested by the Examiner would alter the meaning of the term "substrate" so that it would be inconsistent with its use in the specification and claims and, moreover, so that it would be inconsistent with the term's use in the art.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91 and 103-105 are rejected under 35 U.S.C. § 112, second paragraph. The Examiner alleges that claims 55 and 60 are confusing and ambiguous because it is not clear 1) if the claimed device is a one-piece structure or a two-piece structure; 2) if the substrate is a one-piece device or a two-piece device; 3) what the measurement chamber is; 4) if the microchannel need not be connected to anything but the measuring chamber; and 5) if the measuring chamber need not be connected to anything. Applicants respectfully disagree for all the reasons previously presented in prior responses and traverse the rejection. However, without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claim 55 and 60, from which the remaining claim depend, have been amended, thereby obviating the rejection.

Claims 55 and 60 are now directed to a microfluidic system comprising a substrate, wherein the substrate comprises a single microfluidic structure having at least one measurement chamber, the measurement chamber comprising walls surrounding a base, and wherein the substrate further comprises at least one microchannel with at least one inlet for receiving an aqueous solution and at least one outlet, wherein the outlet opens into the at least one measurement chamber, and wherein the outlet delivers the aqueous solution into the measurement chamber. The present amendments obviate the indefiniteness rejections because 1) the device is a one-piece structure; 2) the substrate is a one-piece device; 3) the measurement chamber is clearly defined in the specification (see page 31, line 25 to page 32, line 10 of the specification); 4) the microchannel has at least an inlet for receiving an aqueous solution and an outlet that opens into the measurement chamber; and 5) the measuring chamber is connected to at least one microchannel.

In addition, the Examiner alleges that in claim 55 the substrate comprises a measurement chamber and a raised aperture, the raised aperture comprises a tip, and the tip comprises a housing. The Examiner alleges that 1) an aperture is not a structure; 2) that it is not clear if the measurement chamber comprises a raised structure and what the raised structure is; 3) that the relationship of the aperture, the substrate, and the measurement chamber is unclear; and 4) how the microchannel delivers different aqueous streams to the measurement chamber, without the streams mixing together. Applicants respectfully disagree. Nevertheless without acquiescing to

the rejection and solely to facilitate prosecution, Applicants have amended claim 55. In the amended claim the substrate comprises a measurement chamber comprising walls surrounding a base (see page 31, lines 25 and 26 of the specification for support) and at least one tip, the tip comprising a housing defining a lumen and an aperture, wherein the tip is raised from the substrate of the walls or base of the chamber, and wherein the substrate further comprises at least one microchannel with at least one inlet for receiving an aqueous solution (see page 47, line 25 and page 58, line 8 for support) and at least one outlet, wherein the outlet opens into the at least one measurement chamber, and wherein the outlet delivers the aqueous solution into the measurement chamber. The present amendments obviate the indefiniteness rejection because 1) the aperture is defined by the housing; 2) the measurement chamber comprises a tip which is raised from the substrate of the walls or base of the chamber; 3) the substrate comprises a chamber and the aperture is defined by the housing of the tip which is raised from the substrate of the chamber; and 4) the channel delivers an aqueous solution to the chamber.

The Examiner alleges that claims 90 and 106 are confusing. Claim 90 recites "[t]he system according to claim 55 or 60, further comprising a scanning mechanism, wherein the cell or lipid based structure is mechanically scanned across stationary microchannel outlets, wherein the microchannel outlets are mechanically scanned relative to a stationary cell or lipid based structure, or wherein a fluid is scanned across an immobilized cell or lipid based structure." The Examiner alleges that it cannot be determined what occurs in the "wherein" clauses of claim 90 because when an object is scanned it means a person moves her eyes across it, or a camera or other imaging device moves across it, to make and possibly record an image of the object. The Examiner alleges that the first full paragraph of page 7 of the specification shows that the word "scanning" has its ordinary meaning. Applicants respectfully disagree.

A scanning mechanism is a mechanism "for changing the position of a cell relative to the outlets of the microchannels." (see specification at page 13, lines 27 and 28). The first full paragraph of page 7 is consistent with this definition because it describes a mechanism for moving either substrate or an electrode device inserted into a cell in an x-, y-, and/or z- direction.

> **Preferably, the system further comprises a scanning mechanism for scanning one or more of the substrate or the electrode device inserted into cell in an x-, y-, and/or z-direction**. In one aspect, the system comprises a processor in

> communication with the scanning mechanism which controls one or more of: the rate of scanning, the direction of scanning, acceleration of scanning, and number of scans. Preferably, the processor provides instructions to the scanning mechanism in response to signals from the detector. The system may further comprise an amplifier in communication with the at least one electrode device for detecting changes in electrical properties of one or more cells. (emphasis added)

Nowhere does the specification describe a scanning mechanism as an imaging system as suggested by the Examiner. Instead, the specification repeatedly describes a scanning mechanism as a mechanism for changing the position of the outlets of microchannels relative to cells.

> In another aspect, the system comprises a scanning mechanism for scanning a sensor (e.g., such as a cell) across the aqueous streams from the channels. (see page 7, lines 19-21).

> In one aspect, a system according to the invention further comprises a scanning mechanism for changing the position of a cell relative to the outlets of the microchannels. The scanning mechanism can translate the substrate containing the microchannel outlets relative to a stationary cell, or can translate the cell relative to a stationary substrate, or can move both cell and substrate at varying rates and directions relative to each other. (see page 13, line 27 to page 14, line 2).

> A scanning mechanism can be used to move both the capillary and cell simultaneously, to maintain the appropriate proximity of the capillary to the cell. (see page 15, lines 6-8).

> Figures 11A-D illustrate a system for scanning a cell impaled with a nanoelectrode across multiple collimated streams containing drug candidates. As shown in Figure 11A, a substrate comprising a plurality of channels which feed into a cell chamber is placed in proximity to a nanoelectrode and holding pipette. Proper positioning of a cell by the holding pipette and/or insertion of a nanoelectrode into the cell can be visualized by making the cell chamber at least partially optically transparent so that light absorbed and/or transmitted by the cell can be measured. The nanoelectrode is used to measure the electrical properties of the cell as it is scanned across microchannel inlets that open into the

cell chamber (see, e.g., as show in Figures 11B-D). (see page 24, lines 17-25)

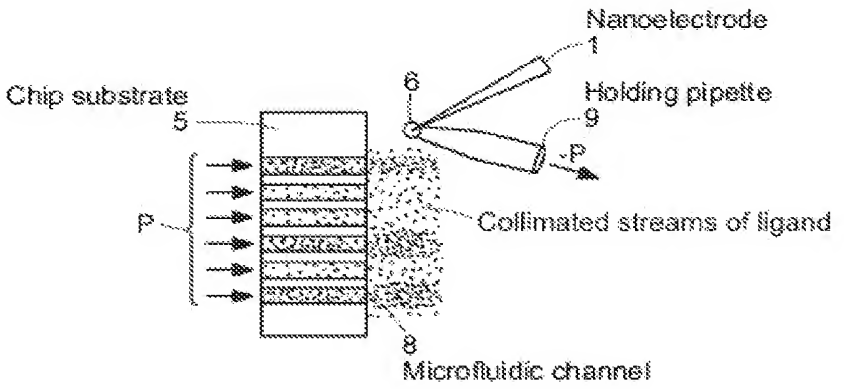

FIG. 11B

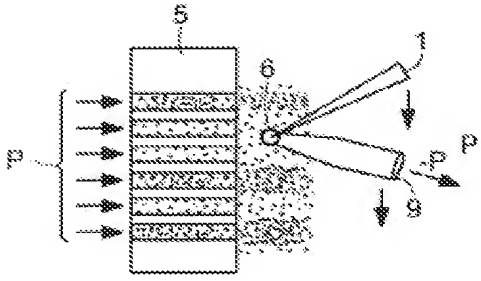

FIG. 11C

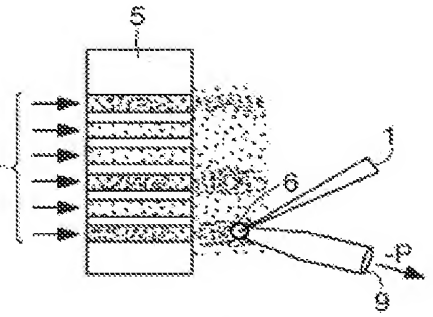

FIG. 11D

Figure 15F is a top view of Figure 15D and shows cell scanning across the "U-turn" fluid streams. (see page 27, lines 26 and 27).

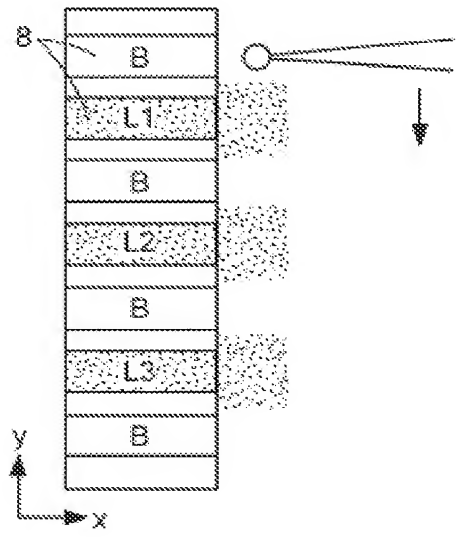

FIG. 15F

The arrows in the Figures indicate directions in which the nanoelectrode-impaled or nanoelectrode-contacted cell(s) can be scanned. (see page 28, lines 2 and 3).

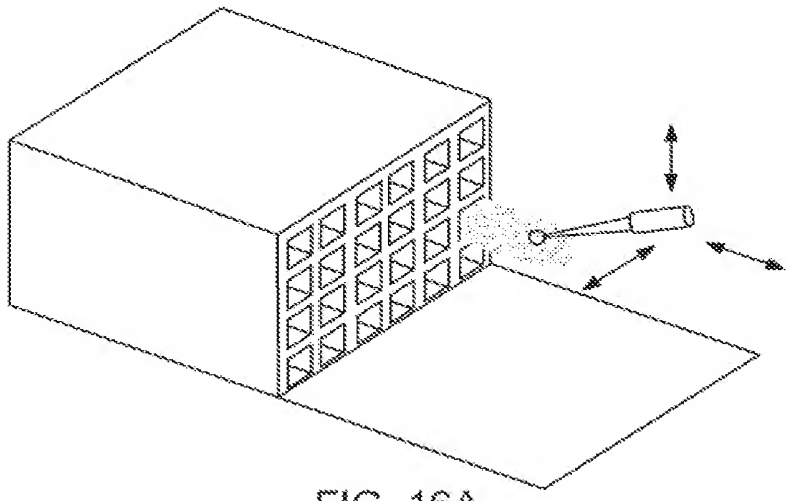

FIG. 16A

Figures 18A-C show mechanical scanning of the nanoelectrode-contacted cell across stationary microchannel outlets. Figures 18D-F show mechanical scanning of microchannel outlets relative to a stationary nanoelectrode-contacted cell. (see page 28, line 29 to page 29, line 2).

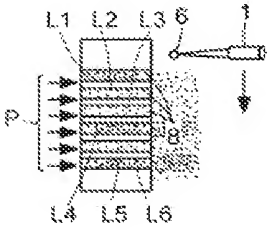

FIG. 18A

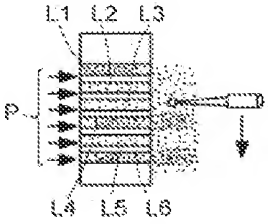

FIG. 18B

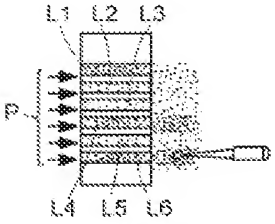

FIG. 18C

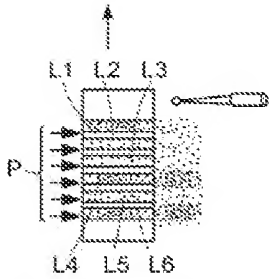

FIG. 18D

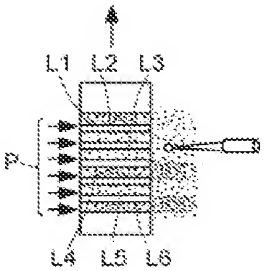

FIG. 18E

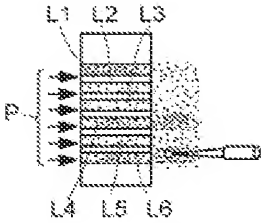

FIG. 18F

In view of Applicants' disclosure, as detailed above, a person of skill in the art would understand that the specification describes a scanning mechanism as a mechanism for changing the position of a cell relative to outlets of microchannels. Nevertheless, without acquiescing to the rejection and solely to facilitate prosecution, Applicants have amended claim 90 to recite "[t]he system according to claim 55 or 60, further comprising a scanning mechanism, wherein the cell or lipid based structure is mechanically moved across stationary microchannel outlets, wherein the microchannel outlets are mechanically moved relative to a stationary cell or lipid based structure, or wherein a fluid is moved across an immobilized cell or lipid based structure." Similarly, claim 106 has been amended to recite "[t]he system according to claim 90, wherein the fluid stream is moved across an immobilized cell by controlled variation of the pressure

across, and flow rates through, each microchannel." Support for the amendments is provided in all of the sections of the specification cited above that describe scanning mechanism as a mechanism for changing the position of a cell relative to microchannel outlets in a substrate.

Rejections under 35 U.S.C. § 103

Claims 55-62, 64, 65, 67, 71, 79, 81, 83, 85, 87, 89-91, and 103-106 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Maher et al. (U.S. Patent Application Publication 2002/0025568 hereinafter "Maher") and He et al. (U.S. Patent Application Publication 2003/0049862 hereinafter "He") in view of Peeters (U.S. Patent No. 6,123,819 hereinafter "Peeters") and Hamill et al. ("Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," Pflugers Archiv 391:85-100, 1981 hereinafter "Hamill").

The Examiner alleges that Maher describes an apparatus for carrying out electrical measurements on cells comprising an array of measurement chambers (a microtiter plate), an array of electrodes arranged in a lid or cover that matches the mircotiter plate, and that the electrodes may be solid or fluid filed. The Examiner admits that Maher does not describe that the measurement chambers have microchannels, but alleges that this deficiency is cured by He. The Examiner alleges that He describes a microfluidic system in which the plumbing is incorporated into the lid for a standard microtiter plate, and thereby provides measurement chambers with microchannels. The Examiner alleges that the claimed microfluidics system is the system taught by Maher as modified by He and that one would have been motivated to combine the teachings of Maher and He because He teaches that this modification transforms the apparatus into a high-throughput apparatus using standard industry equipment. Applicants traverse the rejection.

Claims 55 and 60 have been amended. As amended the claims are directed to a microfluidic system comprising a substrate, wherein the substrate comprises a single microfluidic structure having at least one measurement chamber for containing one or more cells or lipid based cell structures, the measurement chamber comprising walls surrounding a base and at least one tip, wherein the tip is raised from the substrate of the walls or base of the chamber, and further wherein at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate further comprises at least one microchannel with at least one inlet for

receiving an aqueous solution and at least one outlet, wherein the outlet opens into the at least one measurement chamber, and wherein the outlet delivers the aqueous solution into the measurement chamber. None of the cited references, either individually or in combination, teach or suggest a microfluidic system comprising a substrate wherein the substrate comprises a single microfluidic structure because the cited references teach a system that is composed of a microwell plate, electrodes which are attached to a lid for the plate, and microchannels that are also associated with the lid. Furthermore, none of the cited references, either individually or in combination, teach or suggest a microfluidic system comprising tips that are raised from the walls or base of the substrate of a measurement chamber because the cited references teach a device in which the electrodes are attached to a lid of a microwell plate and are inserted into the wells of the plate. Moreover, combining the cited references would not arrive at the claimed system because the claimed system comprises a substrate which comprises a single microfluidic structure. The combined teaching of Maher and He would yield a multi-part device that does not comprise a substrate comprising a single microfluidic structure. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Regarding claims 90 and 106, the Examiner bases the rejection on an incorrect interpretation of the claims. The Examiner asserts that "A scanner can scan the cells, but it cannot move them. The laser scanner and the imaging equipment would have been readily programmed by one of ordinary skill in the art at the time of the invention to detect one or more cells at any desired location within a measurement chamber or within a microchannel and to scan the entirety of the measurement chambers and the microchannels" (Office Action dated July 28, 2010 at page 9). As described in detail above, the scanning mechanism is a mechanism for changing the position of a cell relative to the position of a microchannel outlet. Applicants' specification does not describe imaging equipment nor does it use the term scanning in the imaging context. None of the cited references, either individually or in combination, teach or suggest a scanning mechanism for changing the position of a cell relative to a microchannel outlet. Accordingly, Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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